TRANSCRIPT OF PROCEEDINGS

IN THE MATTER OF:)
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STAKEHOLDERS MEETING WITH)
ProdiGene)
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UNITED STATES DEPARTMENT OF AGRICULTURE

IN THE MATTER OF:)
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STAKEHOLDERS MEETING WITH)
ProdiGene)
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Training Room 1
4700 River Road
Riverdale, MD

Friday
February 27, 2004

The parties met, pursuant to the notice, at 1:34 p.m.

BEFORE: MS. CINDY SMITH
Deputy Administrator

APPEARANCES:

For the U.S. DEPARTMENT OF AGRICULTURE:

REBECCA BECH, Assistant Deputy Administrator
JOHN TURNER
NEIL HOFFMAN
MICHAEL WACH
SUSAN KOEHLER

Meeting with: ProdiGene
DONNA DELANEY, Ph.D., Director,
Regulatory Affairs
JOHN W. REIHER, Chief Executive Officer

PARTICIPANTS:

LEVIS HANDLEY
ROBYN ROSE
MICHAEL BLANCHETTE
CRAIG ROSELAND
MEGHAN THOMAS
HALLIE PICKHARD
JIM WHITE
LAURA BARTLEY

P R O C E E D I N G S

(1:34 p.m.)

MS. SMITH: Welcome to our Stakeholder discussion series on our upcoming environmental impact statement and our revised plant biotech regulations. We want to thank you for taking time from your busy schedules to come here and participate in this meeting with us today, and especially for sharing your thoughts with us.

There are two primary purposes for these meetings that we are conducting this week. The first is to give us an opportunity to share information with you about our plans to develop an EIS and to amend our plant biotechnology regulations.

The second purpose is to get a diverse and informative input, which will support thoughtful and effective decision making on our part in revising our plant biotechnology regulations. We have here from BRS members of our management team as well as numerous members of our staff; and, when available, other key Agency personnel who are supporting BRS in this effort.

I do want to mention two key individuals who have now been dedicated to this effort on a full-time basis in terms of providing full-time management of our work to complete both the EIS and our revised

regulations. The first is John Turner, who you may be familiar with. John is a very important member of our leadership team here in BRS and I am pleased to say that he is leading this effort on a full-time basis.]

The second individual, a new face that you may not be familiar with, is Dr. Michael Wach, a recent BRS hire as an environmental protection specialist within the environmental and ecological analysis unit that Dr. Suzanne Koehler now heads up. In addition to possessing both a Ph.D. and an environmental law J.D., Michael brings research experience in plant pathology in weed science, as well as legal experience in cases involving NEPA, the Clean Water Act, the Clean Air Act and other environmental statutes.

At this point, I am going to turn it over to John Turner to provide you some more background information. When John has completed the rest of our opening remarks, we will just open the rest of time period for your opportunity to make your presentation and ask us any clarifying questions and have any kind of back-and-forth discussion that you would like to have. Thank you.

MR. TURNER: All right, thanks Cindy. As you may know, we have been in discussions with EPA, FDA and the White House; and have coordinated the framework for

biotechnology.

While we have concluded that the coordinated framework, as it stands, has provided an appropriate science and risk-based regulatory approach for biotechnology. The Plant Protection Act of 2000 offers a unique opportunity for APHIS to revise its regulations and potentially to expand our regulatory authority while leveraging the experience that we have gained over the years in regulating in this area. These potential changes could position us well for future advancements in technology.

We concluded those discussions with some general agreement on how our biotech-regulatory approach would evolve. But still there is much opportunity for public and stakeholder input as we move forward to develop the specifics of the regulatory enhancements. So, given this, what we would like to do at these meetings is really to hear from you, to hear your thought and we can follow that with a formal give and take of ideas. It is a unique opportunity for this type of meeting because we are early in the process and since we are not yet in the formal rule-making phase, we are free to speak freely and exchange ideas with stakeholders and the public.

These discussions are being professionally

transcribed. That is for two reasons. The first, so that we have an accurate record of our discussions to facilitate our ability to capture and refer to your input; and secondly, in the interest of transparency and fairness to all stakeholders, we will be making available as far as the public record, potentially on our Web site documentation of all of our stakeholder discussions so that other stakeholders will have the benefit of each of the discussions that we have had during the week.

I want to emphasize that while we are happy to share information on the direction tat we are likely to take, that this thinking is really our current thinking in the process; and during the process, public and stakeholder input, such as the thoughts that we will hear from you will likely influence our thinking, so it is going to be evolving.

In addition, those at USDA, in particular our administrator, the undersecretary, our Office of General Counsel and, of course, the secretary will also be providing insight and direction. While we value your input, it is important to recognize that our thinking will likely evolve so we may have some discussions today about some specific aspect that we seem enthusiastic about but this could change as we go through the

process.

Finally, since it is hard to predict what the final regulations will look like, what we would like to share is our overall priority areas because with these we know that they will be used to set direction and help guide the development and implementation of these new regulations.

The first of these is rigorous regulation, which thoroughly and appropriately evaluate and insure safety and is supported by strong compliance and enforcement. The second is transparency of the regulatory process and regulatory decision-making to stakeholders and to the public. This is really critical for public confidence that we have a very transparent process.

We must have a science-based system, insuring that the best science is used to support regulatory decision-making. This really is crucial to insure the safety. We value communication, coordination and collaboration with a full range of stakeholders. And last, I would mention international leadership. We want to insure that international biotech standards are all science based, as are our own. We want to support international capacity building and we need to consider the international implications of the policy and

regulatory decisions that we make here domestically.

With that, as we begin our instructions, I would just ask that the first time you speak, if you would identify yourself, your name for the transcriber after that. With that, the floor is yours to start with your presentation, or remarks, or whatever you want.

MS. DELANEY: Okay. I think we will start. My name is Donna Delaney and I am going to start with my presentation.

MS. SMITH: You are going to be -- why don't just carry the microphone with you.

MS. DELANEY: Okay. Can I have the next slide please?

First of all, I want to thank you for inviting us here and allowing us to come in and express our ideas in the proposed changes to the regulations. This is really an excellent opportunity for all stakeholders to come and have their voices heard; and, hopefully, to have some influence on the way that the regulations are structured in the future.

Since ProdiGene is a company that specializes in the production of pharmaceutical and industrial protein products in plants, I am going to concentrate my comments on only those two classes. These products differ from other products that USDA regulates in that

the product itself is not the plant, but in most cases is a protein that is purified from the plant material. As such, these products are not agricultural commodities. In most cases, they are generally not intended for food or feed, except in the case edible vaccines.

However, this does not mean that they are inherently less safe and this is going to be a reoccurring theme throughout my talk. These products hold huge potential benefits for society in terms of safer drugs, environmentally friendly industrial enzymes and potential new sources of fuel. However, we realize that they need to be handled responsibility. We believe that the regulations should be science based and that any changes to the regulation should not be motivated by political views of special interest.

Can I have the next slide please?

Probably the central theme of my whole presentation is that the regulation should be based on an analysis of safety and potential risk, which can then be used to determine the confinement conditions. Products should be categorized based on a determination of the level of risk not on end-user markets; and thee categories really are just a first step. Products should continue to be evaluated on a case-by-case basis.

Can I have the next slide please?

Policy should allow for flexibility as the product development advances towards commercialization and this was something that was also mentioned in the *Federal Register*. We want to emphasize that safety, environmental and also for business reasons, we are committed to keeping these products segregated from the food and feed supply. I don't want anything that I say here today to confuse you on that point. We really are committed to keeping the food supply safe.

Lastly, we want to comment on a policy on potentially adventitious presence, which we feel is needed.

Next slide please.

One of the items mentioned in the *Federal Register* was this proposal to change the regulations to create risk-based categories for field testing. We feel that this is a good idea; however, we believe strongly that the category should be based on risk and safety information and not end-user markets. For example, a toxin such as BT, which is used to protect food crops from insects is not inherently safer than a protein intended for use as a pharmaceutical that possibly humans make, or that is already present in the food supply with a history of safe use.

All products should undergo a safety assessment to determine potential risk. In the absence of any information, products would be placed in a high-risk category until sufficient information had been accumulated to justify reducing the risk. A decision tree could be used as an initial starting point to place proteins in a high, medium or low-risk category. But, again, this should not substitute for a case-by-case analysis.

Next slide please.

On this slide, we propose a decision tree that could be used to classify pharmaceutical and industrial products. This is just one decision tree. You may decide to another, or some other method, but we are just proposing this today. And the first question we ask: Is protein naturally present in food, or does it have GRAS status?

If the answer is yes, then you go on to the second question: Are there known problems with this food or protein? If the answer is yes, then it would be placed in our moderate-risk category. If the answer is no, then you go on to the next question: Is the level in plants less than equal to the level in food? If the answer is no, then, again, it is placed in a moderate-risk category. If the answer is yes, then it

is a low-risk protein.

If the answer to the first question is no, it is not present in food and doesn't have GRAS status, then we ask: Is there data to show no adverse affect at levels found in the plant? If the answer is yes, it is moderate risk. If the answer is no, then it would be placed in a high-risk category.

If a particular protein was placed in this high-risk category simply because there was no information available, then, as further studies were done and there was information to justify a reduction in risk, then it might be placed in a moderate- or low-risk category. As I said, a decision tree like this would just be a first cut and then further warrant in-depth analysis would be done later because there could be other mitigating or extenuating factors about each protein that would further identify what risk category was most appropriate.

Can I have the next slide please?

On this slide, we show some examples of different proteins that would fall into these different risk categories. Trypsin is an example of a protein that would be low risk. Trypsin is present in food as a component of meat products. Bovine and porcine trypsin has GRAS status. Trypsin is also made by

humans and is one of the major enzymes produced in the human gut.

There are no know detrimental affects of trypsin in the level in grain is lower the level used in other applications. Other proteins that would fall under this low-risk category would be proteins like aprotinin. Aprotinin is also present in food. It is highly concentrated in the liver, and it would also be present in products like hot dogs and other luncheon meats. Aprotinin is not absorbed by the gut. It is tolerated at very high levels, even intravenously and it also has no homology to any known allergens.

Another protein that would fall under the lowest category is collagen. Collagen is a tremendously abundant protein. It is made by all higher vertebrates. It composes 30 percent of the total protein in the human body, which translates to 6 percent of the body weight. Collagen, which has been heated and hydroxulated becomes gelatin and gelatin, of course, has GRAS status and a long history of safety.

A protein that would fall into this moderate-risk category is the transmissible gastroenteritis virus. The vaccine is, of course, swine. The two components of this vaccine may be present in food but may be present at a lower level. And while there is

some data in use that shows that it is not highly toxic. There has not yet been no observable affect level set for this protein.

An example of a high-risk protein would be a synthetic protein to treat cancer and this would be placed in this category because there would be no information at the start; and also cancer drugs typically have some kind of toxic effect, so there probably would be some safety concerns.

Another item that was mentioned in the *Federal Register* I would say a couple of times was the subject of the commercialization of pharmaceutical and industrial products. We wold like to present our approach as to how this process should move forward.

The product-development process for pharmaceutical and industrial products should be a stepwise ladder approach, in which all products would initially start out under high restrictions, such as the current permit conditions. The restrictions would then be eased as long as more safety information and familiarity with the product was accumulated if the data supported it. We realize that some products with known safety concerns would never progress through the system under deregulation. They would always be produced under confinement conditions.

Confinement protocols for all products then would be raised -- on an analysis of safety and risk.

Next slide please.

The process that is illustrated here -- in the early-development stages all products would start out under high restrictions, such as the current permit conditions. And then early field trials would be used to accumulate data on safety and environmental impact. Unless the data supported it, it might be used later to reduce the restrictions.

As products move into the scale-up phase, the protein would be well characterized, stably inherited and the expression would be well known. If the safety data supported it, restrictions may be reduced to something that was more of a performance based design scanner similar to what -- clearly, that can be seen during the notification.

Again, if the data supported it, it maybe the isolation distance could be reduced. As products move into the commercial phase, the safety of the product would be well known and companies would then be given the option to enter into what we are calling a compliance contract. I will discuss that more in the next slide.

For products with demonstrated low risk,

eventually they may move into deregulation; however, even under deregulation, we don't anticipate that these products would ever be produced without isolation. The production strategy would be something that is more similar to the current identity preservation strategy, such as what is used for white corn or waxy corn.

Now this would be done for purely business reasons to protect the identify, purity of the product.

MR. WACH: Before you go on.

MS. DELANEY: Yes.

MR. WACH: In the middle of your slide when you say the level does that refer to your slide a few steps back where you had low, medium and high, or does this arrow indicating all that was in one of those categories? So are yo starting at --

MS. DELANEY: Well, this particular slide doesn't refer to risk. It refers to the restrictions that has it gone under.

MR. WACH: There is no parallel level between this and your slide a couple of steps back --

MS. DELANEY: No, not really.

MR. WACH: Okay.

MS. DELANEY: Can you slip that in? Good, okay. We realize that some products will never proceed through to deregulation and will always be

produced under government oversight.

In addition, some companies may decide on their own that a particular product doesn't warrant going through this deregulation system, or the deregulation process; and they may decide to produce it as a regulated product all the time.

Next slide please.

The idea of a compliance contract is something that I originally heard about from Dr. Jim White here at APHIS. So I know that it is something that you have at least thought about at some time. The idea is that once sufficient safety data had been accumulated and the product had moved into the commercial phase, companies would be given the option of entering into a five-year agreement with APHIS and their performance would be revised annually.

It is our view that in order to qualify for a system like this, a company should have a tested and approved compliance program that should have been in effect for at least two years, so that any problems could be worked out of it. They should have a comprehensive training program for all personnel involved in the construction of the product. They should have a good recent history of compliance because you wouldn't want poorly performing companies to be

given this privilege.

I am also suggesting that the products go through a food-safety evaluation, either through FDA or, if that mechanism wasn't available, possibly APHIS could evaluate the data. Then, the confinement conditions would be based on the results of this food-safety analysis and they would be tailored towards whatever information was discovered in that phase.

Next slide please.

All contract applicants would be required to perform an environmental-risk assessment or review. The extent of that review would be dependant on the projected acreage. We realize that the markets for some crops are larger than markets for others and what is the commercial scale for one product is not necessarily commercial scale for another.

So the determination of whether a product is in the commercial phase cannot be made based on the acreage that it has been grown on. Yet, we realize that the acreage does affect a product's potential impact on the environment. Products that are grown under low acreage, may require less expensive environmental analysis. We were suggesting similar to what is currently required for permit applications. While there are products that are grown on substantially larger

acreage, they may require more expensive analysis.

Another item in the *Federal Register* was the current lack of a policy on adventitious presence. Despite adherence to rigorous containment protocols, low levels of products not intended for food or feed may be present in commercial crops at some time. A system should be available to evaluate the potential hazard of such an occurrence, such as the food industry is not disrupted and food supply is not compromised or questioned.

An assessment of safety or risk could be made using a safety model. And we will suggest one model here today; and you may decide to use another model and you may decide to use some other technique. But the point that we are trying to make is we would like some kind of science-based analysis.

These safety models are similar to ones that are used for other regulated products that are regulated by FDA and EPA.

Next slide please.

The basic principle behind all safety models is that risk is proportional to hazard times exposure; and exposure is proportional to concentration times time.

Next slide please.

The factors that affect exposure are the probability of intermixing with food crops during production. This would occur by pollen flow. Intermixing can also happen after harvest in various handling steps. You should also consider the probability of out-crossing with related weedy species. The frequency of potential exposure -- in other words, is it a one-time exposure, or repeated exposure.

For adventitious presence, it would most likely be a one time or limited exposure. The amount of potential exposure which relates to the expression level in the plant tissue; the environmental exposure, which one factor is: how many acres is it grown on? Does it represent a new exposure, or has the population been exposed by other means, either to food supply or by exposure to environmental organisms? Will the population be exposed to an active protein or an inactive protein?

Proteins can be inactivated through various food-processing steps. Also, it may be that the actual expressed sequence was an inactive precursor and that should be taken into account.

Next slide please.

Factors that affect the hazard are the toxicity of the protein, the levels shown to have no

detrimental effect. This is, in other words, the no-observable adverse affect level. This is the highest concentration at which no adverse affects are observed. The potential allergenicity: Is the protein already in the food supply? If it is, then there may be safety data available.

Does a protein have GRAS status for its uses? Is the protein made by humans or animals and this goes back to the allergenicity issue. Does it constitute a new exposure? Is there experience and knowledge of the protein and its known affects and how similar is it to other known proteins?

Next slide please.

The model that I will present is one that was developed by Dr. John Howard and Dr. K.C. Donnelly at Texas A & M. It basically consists of a hazard quotient that is equal to the cumulative intake, which is a measure of exposure divided by the referenced dose, which again is the maximum dose at which no adverse affects are observed.

Next slide please.

The exposure is calculated as this cumulative intake and it is related to a number of different factors, one of which is the concentration in the food, which is composed of the expression level in the plant

and a containment factor which refers to the isolation conditions that were used in the field. This is a measure of the percentage of out-crossing that may have occurred in the production.

The inactivation factor is a measure of the proportion of the protein that may have been inactivated through food-processing steps. The ingestion rate is the typical dose of that food product that is eaten on. The exposure frequency is the typical number of times that that food product is eaten and then the body weight.

The reference dose is calculated as this no observable adverse affect level, which again is the last level at which no adverse affects are observed. That is divided by an uncertainty factor and this was put in the model to account for any extrapolations in the data, such as if you were taking data that was accumulated on animals and then transferring that to humans.

Next slide please.

If we solve the equation, then, for the containment factor, again containment factor relates to the isolation conditions in the field. So that kind of goes back to the question of adventitious presence. This is the equation that we end up with.

A containment factor greater than one

indicates that your exposure is less than your no observable adverse affect level. In that case, there would be no safety concerns and no containment would be necessary. Although, as I said, we don't advocate producing these types of products without containment. But this would just -- if an unintended exposure did occur, the model would supply some assurance that there would be no safety danger.

A containment factor less than, or equal to one indicates that some kind of containment is needed. Then, depending on the value of this factor, we would devise an isolation protocol that would meet that requirement.

Next slide please.

To illustrate the model, I am going to use an example of the protein aprotinin. Aprotinin is a serum protease inhibitor. It has pharmaceutical applications in the treatment of patients undergoing pulmonary bypass surgery where it is used to reduce blood loss. It is also a component in wound-closure cases. It has industrial applications also in cell culture.

Now, if we use this equation for the containment factor again and we use the following assumptions, we say that the body weight is 70 kilograms, the no-observable affect is 125 milligrams

per kilogram. This is based on -- certainly, in the literature, it was a dog injection study. Since this is an injection study and we are really trying to make some assumptions on all toxicity, this is really a very conservative estimate of the no-effect level because since we know that aprotinin is not absorbed by the gut, the no-affect level in terms of oral toxicity would likely be a much higher number.

The ingestation rate for pharm is one ounce or .03 kilograms, which is equivalent to one whole breakfast cereal. The exposure frequency is a 16 ounce box of cereal, or 16 doses. The inactivation factor is .1. We are assuming that 90 percent of the protein is inactivated during the processing of that cereal. We are assuming an uncertainty factor of a 100 and that is to account for the fact that this is a dog study and we are translating that to humans.

Also, this is an injection study and we are really looking at oral toxicity, so a factor of 10 for each one of those uncertainties.

The expression level on corn we know is 100 milligrams per kilogram, as you have seen.

Now, if we plug all those numbers into the equation for containment factor, we arrive at a containment factor of 18, which is greater than one and

in that case, there would be no safety concern and no containment required.

Even if we consider that the product was eaten raw. In the words, the inactivation factor was one. It was not inactivated at all. If we plug that in, we would still end up with a containment factor of 1.8, which again is greater than one, and it indicates that there are no safety concerns.

Now, while we don't advocate, there are only aprotinin in corn without isolation, again, it would provide some information that if an unintended exposure did occur that there would be no safety danger.

The model as we have used it in the last example is really a measure of oral toxicity. Another concern in terms of exposure is the antigenic potential of that protein. We have determined based on a mouse study, that no observable affect level, in terms of antigenic potential for aprotinin, is .3 milligrams per kilogram. In other words, mice fed .3 milligrams of aprotinin per kilogram or less did not develop antibodies to this protein.

So if we plug this number into that equation, we end up with a containment factor of .04, which indicates that some form of containment is needed if antigenic potential is a concern. Then we would devise

a containment strategy such that no more than four percent of any neighboring fields were contaminated.

Now, in reality, we would probably go for a much more conservative isolation protocol than that. We would make sure that much less than four percent was contaminated.

Next slide please.

Lastly, we just wanted to talk about a few other miscellaneous issues that were mentioned in the *Federal Register* notice. One of those is changes relative to environmental review of pharmaceutical and industrial products. Let me see that again.

Pharmaceutical and industrial products are currently grown on very small acreage. Many of these products are safe. They have no selective advantage in nature. They have no phenotypic effects, so they have little or no impact on the environment.

Also, permanent requirements require that the destruction of crop residue after harvest and this further reduces the potential impact on the environment. Environmental assessment is already required as part of the permit-application process and we feel that it is appropriate as is for the acres that are being grown. However, if acreage were to increase substantially, then an additional evaluation should be

performed as warranted.

Another issue that was mentioned is the question of whether pharmaceutical and industrial products that are produced in food crops should be regulated differently than those that are produced in non-food crops? When you think about it, the requirement for containment and isolation for food and feed is the same whether it is a food crop or a non-food crop.

All companies producing these products are committed to keeping them out of the food supply. The question that already exists for using food products produced. Pharmaceutical, for example, eggs and yeast are already used to produce vaccines. So this conflict of using food products to produce pharmaceuticals is not a new one.

Next slide please.

Also, both food crops and non-food crops, are both agricultural products. Non-food crops can be grown on the same land as food crops, so the possibility of intermixing from volunteers that come up on the surface contain seeds that is the same for both. Also, the same equipment can be used for both types of crops. So the need for dedicated equipment is the same whether it is a food crop or a non-food crop.

Where the two differ is in this likelihood of intermixing with food or feed. Food crops, by their very nature, already have a higher probability of inadvertently becoming funneled into the food-procurement infrastructure. For that reason, requirements for containment and isolation should be based on the likelihood of intermixing with food or feed. This will be dependent on the particular crop and will also be dependent on a particular company's production procedures.

Another issue is the issue of: Food-safety evaluation for pharmaceutical and industrial products and whether that should influence the permit conditions? As we have already stated, we think that a food-safety evaluation is an excellent idea. The information could be used to set containment requirements. It would also provide needed information in the event of an accident or release. And this information could be used to provide a scientific basis for analyzing the potential risk.

It would also provide a science-based criteria upon which to base the permit conditions.

In summary, we just want to say that we support the Agency in its review process. Our goal is the safe and efficient development of these products

for the benefit of society. We are committed to keeping these products out of the food supply. We feel that the regulations should be science based and founded on a risk-assessment analysis. The product should not be categorized based on their market class or intended use.

Next slide please.

The requirements for containment of plants and materials should be judged by how they affect the potential risks. We feel that a policy on potential adventitious presence is necessary and should be based on a scientific analysis of the risk.

Finally, we want to say that we remain committed to compliance and we support the Agency's oversight and enforcement of the regulations.

Again, I want to thank you for letting us come in and express our ideas. I hope that this will generate some discussion and we can get some feedback from you on what we have presented.

MS. SMITH: Thank you. Certainly, you are one of the most prepared organizations that we have had in any of our sessions.

MR. REIHER: This is John Reiher with ProdiGene. Just a reminder, too, if there a slide that you would like us to go back to to look at further, we can certainly do that.

MS. KOEHLER: Actually, I had a question on one of them. On the equation you had, your uncertainty factor would make a very large difference in your outcome. I was wondering in particular with that model that you choose, those two numbers, the 10 and 10 for each.

MS. DELANEY: According to Dr. Howard, who developed the model, that is the standard method of assigning these uncertainty factors. There is a factor of 10 for each extrapolation of the data, if you will. that is how we came u with the one hundreds. It was a dog study that we were translating to humans and it was a factor of 10. Then in an inaction study, we are really looking at oral toxicity; and 10 x 10 is 100. That is how we came up with it.

MS. SMITH: Do you have any questions for us in terms of clarifications in what we meant in the notice of intent, or other comments that you want to make?

MS. DELANEY: Well, I would simply ask: What are your thoughts on what we have presented here today? Are we way off base, or is that somewhere in the line of what you were thinking or what?

MS. SMITH: Well, you presented a lot. I would say that there were points that you made that I

was thinking to myself: It is almost like they were in the room with us in some of our recent discussions. So I think some of our thinking is similar; and then, clearly, there are some new ideas that you have proposed here that are not included in the kinds of discussions that we have had as far as I know.

MR. REIHER: One of the areas that Donna spent a fair amount of time on in her presentation was the interest that we would have in having the types of products that we produce not be categorized due to application or market use, but actually be grouped according to actual risk level, which is a key element to this presentation.

MS. SMITH: We appreciate that point and Monica thinks that we could clarify in terms of our notice. While our notice refers to the different categories, our intention there really was to just give examples of what we saw -- certain crop combinations could fall into certain categories.

We do recognize that for pharmaceutical and industrials that there are members of that group that pose much less risk than other members. So one of the things that we have talked about, for example, is just because you bring something in at a certain level of risk that doesn't mean that it stays there. That after

the review, then the results of the analysis that we do in the review that could send that to a different level within the system.

I think I saw that actually in your presentation as well.

MS. DELANEY: Good.

MR. WACH: One additional comment about your decision tree is that goes a way of evaluating the risk associated with the product. But we don't necessarily evaluate it at that level. One additional layer of analysis that may go into that is if a proposal would come to us from a company that we never heard of before due to being a start-up and there are proposing, by your decision tree, may be a medium risk product but we have no data on their history or their ability to actually do this sort of study that may add another layer of our analysis as to what the real risk of that particular proposal is.

MS. DELANEY: Right. You have an uncertainty about the company connecting in itself, yes. I can appreciate that.

MR. WACH: That could be -- I guess if you feel that your model can accommodate that or at least you are suggesting that this a model --

MS. SMITH: Well, the decision tree that I

presented, no, that doesn't account for that at all. But that is what I say that that is really just a first cut and a case=by-case analysis should follow. Those things would come up in that kind of an analysis.

One of the things that I didn't mention in the talk that we had a question on was this Item 5 in the *Federal Register* on your consideration of regulation of non-viable plant material under the noxious weed structure. Can you go into that a little bit just in terms of clarification. If you look at the definition of noxious weed under the noxious weed that already is in the Plant Protection Act of 2000. Just the distinction between that and the Plant Pest Authority, which we operate under now is that under the Noxious Weed Authority, we could have the ability to regulate not just a plant but also plant products.

We have that in the notice. We don't have any particular intention in mind necessarily along those lines but we really are just kind of sensitizing the public and stakeholders to the fact that that is a distinction in terms of that authority. So that is something that we would appreciate receiving comments about. How we should consider whether we should leverage that authority or not?

MS. DELANEY: Would you agree that in a

sense non-viable plant material is already regulated because we are required to keep it out of the food and feed supply?

MS. SMITH: I think what we are looking at is: If we wanted to look at any of that a little bit differently than we are currently.

MS. DELANEY: In other words --

MS. SMITH: And any requirement -- but that still is very open. So we would be looking for comments to help us kind of identify what the consideration should be, when should it be considered to be regulated as opposed to whether we should leverage that authority as to claim that we would not.

MS. DELANEY: Okay.

MR. REIHER: We paid particular attention to that. As some of you are aware of, one of our processing steps is to really devitalize material as quickly as possible once it is harvested to really reduce down-stream effects. So non-viable material is obviously an area of interest for us in how and if that would be looked at differently in the future.

MS. SMITH: One of the things that we do that will have to factor into our regulation implementation is what kind of a transition if there are things that are acceptable at this point under our regulation that

would not be n the future, or any aspect of our regulation that would change, we would have to look at what the transition will be to that change.

MS. DELANEY: Can yo give us some idea of your impression of how the commercialization of pharmaceutical and industrial products should proceed?

MS. SMITH: How we think it should proceed?

MS. DELANEY: Yes.

MS. SMITH: Well, I don't know if I will tell you how we think it should. I could give you a couple of options.

MS. DELANEY: Okay.

MS. SMITH: One option to consider is: Whether a pharmaceuticals and industrials could meet the same safety criteria that is part of the deregulation process. If they can meet that safety criteria, then they could qualify for deregulation.

As reflected in question No. 6, another option that we are considering is: Whether there should be some different mechanism that is not currently in place, such as the compliance contract approach where we consider the fact that there is going to need to be a long-term conduct in these field tests that similar growth is done year after year and try to have a process that is more efficient for commercialization.

So some of the ways that it might be more efficient is understanding what your long-term plan is for that growth and evaluating a proposal that tells us what the long-term plan is? What you are going to do for five years rather than just this first year? And then our evaluation would be something that also considers that long term. So rather than us like repeat a full evaluation every year, we do a full evaluation in the first year and then in subsequent years, we may be looking at additional information that you would provide us that you learned through the course of your conduct of growing your materials.

Another thing that we want to look at -- I think there is an opportunity that increased transparency. We want to honor confidential business information, of course, as is required. but we also recognize the public has a lot more interest in understanding what is happening with pharmaceuticals and industrials. so what we would want to look at in this mechanism is: Is there a way to increase transparency? Is there some information and a format that we can make as part of the requirements that you might provide us about your long-term plan on what you are growing, as well as the corresponding safeguards that will insure confinement that we can make available

to the public let's say on our Web site? So that there is more transparency to the system without jeopardizing your confidential business information.

Essentially, we are looking at what a new mechanism might look like. And that is the kind of comments that we would appreciate hearing.

MS. DELANEY: Would that be something similar to a drug master file or not that detailed? Is that the kind of information that you are talking about putting on your Web site, specific information about a product for the public?

MS. SMITH: At this point, we really are just in the beginning stages of identifying of what that would look like. So we welcome any comments that you have along those lines.

MR. TURNER: Not highly technical, something for the public that would explain to them what the product is, what it is supposed to be used for?

MS. DELANEY: Kind of in layman's terms.

MR. TURNER: In layman's terms and everyone could benefit if they understood the safeguards also.

MS. DELANEY: Right.

MR. TURNER: All of the things that are in place. It could do a lot for public confidence in answering their questions and possibly demystifying

this to some extent. The idea was to move to something that is more efficient and effective. When it becomes operational and standard procedures, the same things over and over, and will increase the transparency.

MS. DELANEY: Yes. Okay.

MR. REIHER: You mentioned the potential of deregulation for these products. Although that certainly would be a long-term goal and could very much be a long-term reality in some cases, that would severely limit the upstream opportunities for some of these areas, just given the market size and the time to capture some sort of market potential. I would just like a comment on the deregulation?

MS. SMITH: Do you want to tell us a little more about that?

MR. REIHER: Well, certainly some of these products could become deregulated based on their inherently low level of risk. There are others that the determination of that level of risk, the cost and time associated with that just simply may be prohibitive to an entity trying to bring them forward. It could be quite a limiting factor.

MS. SMITH: Thank you.

MS. DELANEY: And I think that that was the whole point about the item in the *Federal Register* that

brought up the point that there should be some mechanism for commercializing these products under government oversight that you mentioned.

MR. TURNER: That is a good comment. We have talked about a range of options there that might be more cooperative route.

MS. DELANEY: Right. Also there may be some products that maybe just don't meet the safety criteria for deregulation, but they are still commercial opportunities and they are still maybe produced commercially. It is just that they would have very strict confinement conditions.

I think that was about all I had.

MR. REIHER: Really any other comments or questions, we would be happy to elaborate on any of the information that we have presented. We did try to present a host of items. Hopefully, some of which will have merit and be worthy of further discussion. We feel as though we have a significant amount of experience in this field and have certainly come quite a distance in terms of our compliance program and level of training in those things that we do.

MS. SMITH: Thank you. do we have more questions?

MS. KOEHLER: Yes, just a couple of points.

In your presentation, there was a place in there where you used the term "environmental assessment" and I just want to be clear in what context you were using that and the formal NEPA term of the prepared preparation of environmental assessment, that did not seem to be what you were intending.

MS. DELANEY: No, that is not what I was intending. I am not intending to deal with a full-blown environmental impact statement. Just more of a review of the effects and the issues related to the environment.

MS. KOEHLER: Okay. You may just want to make a note of that. Are you going to leave a copy of your presentation with us?

MS. DELANEY: I can.

MS. KOEHLER: That would be helpful.

MS. DELANEY: Okay.

MS. KOEHLER: The other thing I noticed is that your model did not appear to directly address the potential impacts to non-human, non-target organisms, so the potential for impact to wild life here. Your model first asks the question about food safety and there didn't appear to be a particularly place in there where you are asking: Well, what are the impacts to other non-targeted organisms, which potentially might occur if you have

wild life coming in and grazing on your PMPs. I was wondering if you had any comments on that?

MS. DELANEY: Well, you can alter the different -- like, for example, inactivation practice -- if a wild animal was eating that product raw, then the inactivation factor would be one. It would be one inactivation. So you can account for things like that in the model.

I think that that model is really only as good as the information that you put into it; and it is only as accurate as the assumptions that you make. The more accurate the figures are that yo can put into it, the more useful it will be.

MR. REIHER: Things like body weight, obviously could be changed as well, and frequency.

MS. DELANEY: Right. When I was practicing this, a couple of people asked me: Well, what about children? Certainly, kilograms is a lot more than any child would weight and maybe you want to be calculating a more sensitive exposure to the potential impact on children. That is an adjustment that you can make and you can just put a lower body weight in there and you can do several calculations and then look at the range of figures that you get and make some kind of generalization from there.

MR. ROSELAND: As a follow-up to that quite general question. You realize how useful having safety data would be for us as we determine the containment level that is necessary.

MS. DELANEY: Yes.

MR. ROSELAND: And also as you think about the longer-term prospects in which we -- if you are looking to deregulation, then the safety data is something that we would use. In the EPA tests, for example, you were looking at the effects of these materials on birds and vertebrates and so forth and so on. I was just wondering whether knowing the relevance and importance, whether ProdiGene is pursuing any of that data of that position itself?

MR. REIHER: Well, for example, the expression level in plant tissue and some of those pieces of information, some of which we have. Others we are pursuing, so we continued to either develop or acquire the kind of data that would support an accurate, or more accurate, risk level, as opposed to just a kind of a broad categorization of the plant producing a particular protein.

From a commercial standpoint and from a business standpoint, the challenge for some of that work is due to the nature of the product that is being

produced and the length of time and the expected level of business hat may be attained at some future point. Some products, obviously, would warrant greater effort towards those ends than others.

MS. DELANEY: Also, many of the products that ProdiGene is currently working on are very safe. Some of them are already in the food supply and we really don't feel like there are any safety concerns as far as wild life. Some of the products that we worked on are on the more experimental level, some of the vaccine products for example. That probably wouldn't be the case if we were ever to develop this in commercial products, we would definitely do some more extensive studies.

MS. SMITH: Any other questions? Well, this has been very informative and we really appreciate your preparation and the information that you have shared with us. We look forward to interacting with you more during this process.

MS. DELANEY: Good.

MS. SMITH: Thanks a lot.

MS. DELANEY: Thank you.

MR. REIHER: Thank you.

MS. SMITH: If the staff can stay, we will go ahead and do a debrief right after this and then we can

take a quick break before our 3:00 o'clock, unless you need to just run out real quick.

(Whereupon, at 2:33 p.m., the meeting in the above-entitled was concluded.)

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REPORTER'S CERTIFICATE

CASE TITLE: STAKEHOLDERS MEETING WITH ProdiGene

HEARING DATE: February 27, 2004

LOCATION: Riverdale, Maryland

I hereby certify that the proceedings and evidence are contained fully and accurately on the tapes and notes reported by me at the hearing in the above case before the United States Department of Agriculture.

Date: February 27, 2004

Renee Miskell

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